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Randomized evaluation of fibrinogen versus placebo in complex cardiovascular surgery: *post hoc* analysis and interpretation of phase III results

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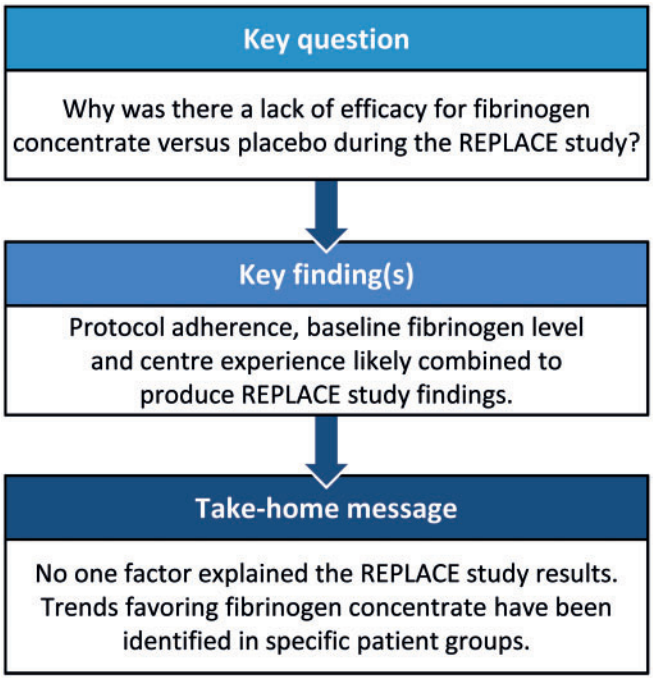

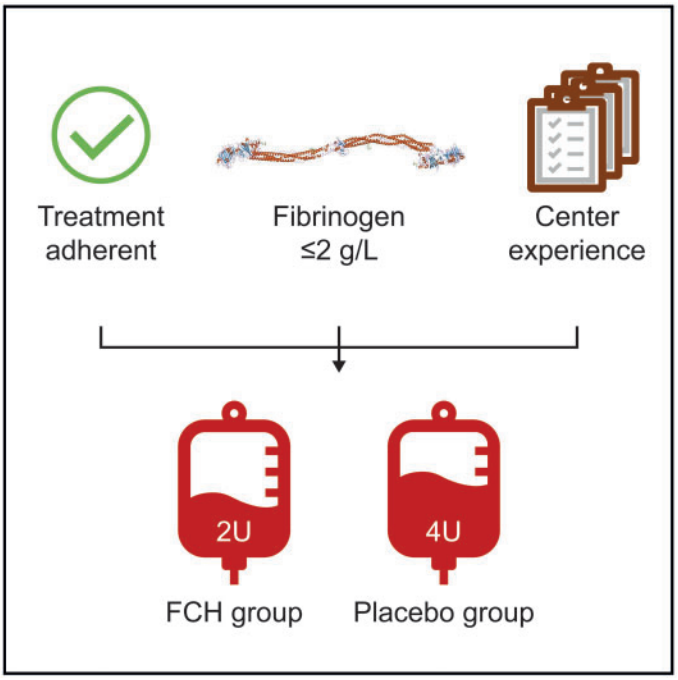

Abstract

OBJECTIVES: In a multicentre, randomized-controlled, phase III trial in complex cardiovascular surgery (Randomized Evaluation of Fibrinogen vs Placebo in Complex Cardiovascular Surgery: REPLACE), single-dose human fibrinogen concentrate (FCH) was associated with the transfusion of increased allogeneic blood products (ABPs) versus placebo. *Post hoc* analyses were performed to identify possible reasons for this result.

METHODS: We stratified REPLACE results by adherence to the transfusion algorithm, pretreatment fibrinogen level (≤2 g/l vs >2 g/l) and whether patients were among the first 3 treated at their centre.

RESULTS: Patients whose treatment was adherent with the transfusion algorithm [FCH, $n = 47$ (60.3%); placebo, $n = 57$ (77.0%); $P = 0.036$] received smaller quantities of ABPs than those with non-adherent treatment ($P < 0.001$). Among treatment-adherent patients with pretreatment plasma fibrinogen ≤2 g/l, greater reduction in 5-min bleeding mass was seen with FCH versus placebo (median -22.5 g vs -15.5 g; $P = 0.071$). Considering patients with the above conditions and not among the first 3 treated at their centre (FCH, $n = 15$; placebo, $n = 22$), FCH was associated with trends towards reduced transfusion of ABPs (median 2.0 vs 4.0 units; $P = 0.573$) and greater reduction in 5-min bleeding mass (median -21.0 g vs -9.5 g; $P = 0.173$). Differences from a preceding single-centre phase II study with positive outcomes included more patients with pretreatment fibrinogen >2 g/l and fewer patients undergoing thoracoabdominal aortic aneurysm repair.

CONCLUSIONS: None of the patient stratifications provided a clear explanation for the lack of efficacy seen for FCH in the REPLACE trial versus the positive phase II outcomes. However, together, the 3 factors demonstrated trends favouring FCH. Less familiarity with the protocol and procedures and unavoidable differences in the study populations may explain the differences seen between the phase II study and REPLACE.

Clinical trial registration: NCT01475669 https://clinicaltrials.gov/ct2/show/NCT01475669; EudraCT trial no: 2011-002685-20.

Keywords: Blood coagulation • Cardiovascular surgical procedures • Fibrinogen • Haemorrhage

INTRODUCTION

Bleeding after cardiac surgery is commonly managed with allogeneic blood product (ABP) transfusion [1]. Complications after surgery may be caused by continued bleeding, and/or ABP transfusion (e.g. volume overload) [2, 3]. Using coagulation factor concentrates instead of ABPs may enable lower infusion volumes, more rapid infusion, higher peak concentration levels, and reduced risk of pathogen transmission or exposure to antigens [4–7].

Fibrinogen plays a critical role in clot strength and bleeding [8–10]. Fibrinogen concentrate human (FCH) supplementation reduces bleeding and the need for ABP transfusion in cardiovascular surgery [11–14] and other settings [15–19]. In the United States, FCH is not licensed for treatment of bleeding in patients undergoing cardiovascular surgery who do not have congenital fibrinogen deficiency.

A recent multinational, randomized clinical trial, REPLACE, unexpectedly found that FCH treatment led to increased ABP transfusions among patients undergoing complex cardiovascular surgery [20]. The study design was based on a successful phase II, single-centre study [12]. The safety-related results were consistent with results from previous studies; percentages of patients with adverse events were similar in both study groups, and thromboembolic event rates were similar in patients receiving FCH versus placebo. Owing to these safety results and the fact that no new safety concerns were identified, it was deemed that rapid infusion of FCH was well-tolerated.

Randomized clinical trials in perioperative bleeding are notoriously difficult to perform. Adherence to transfusion algorithms used to standardize bleeding management across centres, surgical preference and several other variables may influence outcomes despite randomization.

This paper reports secondary analyses of REPLACE. The objective was to identify possible reasons for the finding that FCH was associated with an increase in transfusions of ABP.

MATERIALS AND METHODS

The methods used in the REPLACE trial have been published previously [20]. It was a phase III, prospective, multinational, multicentre, randomized, double-blind, placebo-controlled study (NCT01475669; EudraCT trial no. 2011-002685-20) conducted between 23 January 2012 and 11 September 2014. The study followed International Conference on Harmonization Good Clinical Practice guidelines and approval was obtained from the ethics committee or institutional review board at each centre. Signed informed consent was obtained from patients before participation.

Patients eligible for inclusion were those undergoing elective open surgical procedures on any part of the aorta requiring cardiopulmonary bypass (CPB) (including left heart bypass, with/without other cardiac procedures, e.g. valve replacement/repair, coronary artery bypass grafting), provided they demonstrated a 5-min bleeding mass (5-min BM) of 60–250 g. Exclusion criteria included patients undergoing emergency aortic repair surgery, reoperative aortic surgery at the same anatomical site as the original procedure (e.g. replacement of a previously placed aortic graft; resternotomy and rethoracotomy were permitted), patients undergoing operation for infection and patients with congenital or acquired coagulation disorders.

FCH (RiaSTAP®, CSL Behring, Marburg, Germany) or placebo was administered if a 5-min BM of 60–250 g was observed after cessation of CPB, administration of protamine and establishment of surgical haemostasis. A standardized transfusion algorithm was followed if a 5-min BM after study medication was ≥60 g, with first-round administration of platelets (if platelet count $<100 \times 10^3/\mu l$; dose, 1 U) or fresh-frozen plasma (FFP; dose, 4 U) and second-round administration of FFP or platelets (whichever was not administered previously) (Fig. 1). In patients with persistent bleeding, further treatment comprised 2 U FFP and 1 U platelets. Red blood cells were administered to patients with haemoglobin <7 g/dl, end-organ ischaemia, acute blood loss, or other patient-specific conditions. Further treatment with FFP and platelets was given as required until the 5-min BM was <60 g.

The primary end point was the total number of units of all ABPs (FFP, platelets, red blood cells) given during the first 24 h after administration of the study medication. Secondary end points included a second 5-min BM (after study medication administration) and a difference between the first and second 5-min BM.

The unexpected study outcome was explored using *post hoc* analyses by stratifying results in 3 ways. Firstly, patients from the intent-to-treat population whose treatment was fully compliant

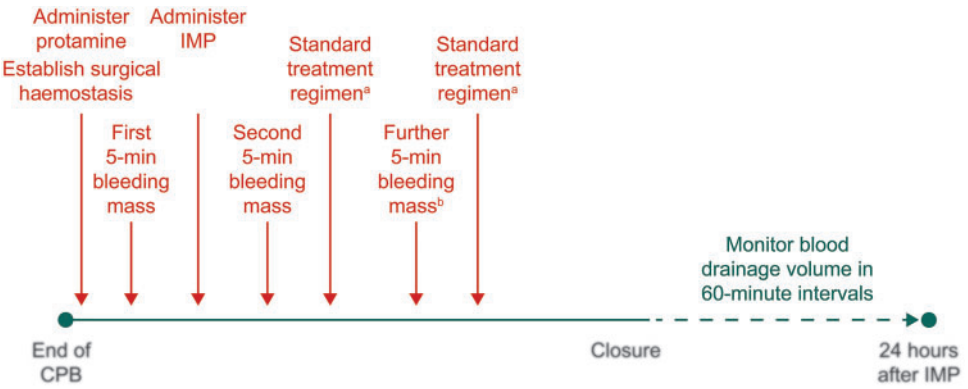

Figure 1: Study protocol—sequence of treatments to control bleeding during REPLACE. [a]Fresh-frozen plasma and/or platelets to be administered according to standard treatment regimen. [b]Repeat cycle of 5-min bleeding mass and standard treatment regimen until bleeding is controlled. CPB: cardiopulmonary bypass; IMP: investigational medicinal product.

Table 1: Transfusion of allogeneic blood products and 5-min BM measurements according to adherence to transfusion algorithm

	ITT		CTA		Non-CTA	
	FCH (*N* = 78)	PBO (*N* = 74)	FCH (*N* = 47)	PBO (*N* = 57)	FCH (*N* = 31)	PBO (*N* = 17)
Allogeneic blood products, 24 h (median units transfused)	5.0*	3.0	3.0**	1.0**	11.0	9.0
First 5-min BM (g), median	107.0	91.0	100.0	85.0	107.0	98.0
Difference between FCH and PBO in median first 5-min BM (g)	16.0		15.0		9.0	
Second 5-min BM (g), median	78.0	72.0	67.0	64.0	87.0	78.0
Difference between FCH and PBO in median second 5-min BM (g)	6.0		3.0		9.0	
Change in 5-min BM (second – first measurement) (g), median	-20.0	-19.5	-21.0	-19.0	-8.0	-21.0
Difference between FCH and PBO in median 5-min BM reduction (g)	-0.5		-2.0		13.0	

*$P < 0.05$ vs placebo.

**$P < 0.001$ vs non-completers.

5-min BM: 5-min bleeding mass; CTA: patients whose treatment was adherent with transfusion algorithm; FCH: fibrinogen concentrate human; ITT: intent-to-treat; non-CTA: patients whose treatment was not fully adherent with the transfusion algorithm; PBO: placebo.

with the transfusion algorithm were defined as 'completers' of the transfusion algorithm (CTA patients). Patients not treated according to the algorithm were classified as non-CTA. The second stratification was by pretreatment fibrinogen level, ~20 min before cessation of CPB (≤2 g/l or >2 g/l; 2 g/l threshold was chosen because international guidelines on bleeding recommend fibrinogen supplementation when fibrinogen levels are <2 g/l [21, 22]). Thirdly, patients were stratified according to whether they were among the first 3 to be treated at their study centre ('early' patients), to account for potential errors as the staff at the sites became familiar with the protocol. The original intention was to include 6–8 sites; because of lower-than-expected recruitment, more sites were added and multiple sites were pooled for rank-sum score analysis.

Differences between CTA and non-CTA patients were analysed using Fisher's exact test. All other statistical analyses were performed using the Wilcoxon rank sum score test.

Given the disparity in results between the phase II study and the phase III REPLACE study, a narrative comparison of patient demographics at entry (including surgical procedure undertaken and baseline fibrinogen) and the timing of the first and second bleeding mass [mean, standard deviation (SD)] was performed. Implications of quantitative and qualitative differences between the study cohorts are discussed, and conclusions regarding the influence of these factors on final study results are based on author expert opinion.

RESULTS

In total, 152 patients received treatment (FCH, $n = 78$; placebo, $n = 74$) and 142 completed the study. Baseline characteristics were similar across both groups: mean age, 64 years; mean body mass index, 26 kg/m^2; the mean Transfusion Risk Understanding Scoring Tool score was 2 in both groups. Surgery involved repair of a thoracic aortic aneurysm in most patients (FCH, 96%; placebo, 95%). Mean plasma fibrinogen levels before surgery were comparable (FCH, 3.03 g/l; placebo, 3.06 g/l), but the median first 5-min BM was higher in the FCH group [FCH, 107.0 g (interquartile range 76.0–138.0 g); placebo, 91.0 g (71.0–112.0 g)]. Although not significant, the decrease in the 5-min BM needed to meet the criterion for stopping treatment (<60 g) was numerically 50% greater in the FCH group than in the placebo group (i.e. from the pretreatment median value, reductions of 48 g and 32 g were needed for stopping treatment in the FCH and placebo groups, respectively).

Table 2: Transfusion of allogeneic blood products and 5-min BM measurements according to pretreatment fibrinogen level and adherence to transfusion algorithm

	Plasma fibrinogen ≤2 g/l						Plasma fibrinogen >2 g/l					
	ITT		CTA		Non-CTA		ITT		CTA		Non-CTA	
	FCH (*N* = 51)	PBO (*N* = 51)	FCH (*N* = 28)	PBO (*N* = 38)	FCH (*N* = 23)	PBO (*N* = 13)	FCH (*N* = 25)	PBO (*N* = 20)	FCH (*N* = 17)	PBO (*N* = 16)	FCH (*N* = 8)	PBO (*N* = 4)
Allogeneic blood products, 24 h (median units transfused)	5.0	4.0	3.0	1.5	11.0	9.0	5.0	0.0	4.0	0.0	11.0	8.0
First 5-min BM (g), median	107.0	94.0	107.5	85.0	107.0	115.0	107.0	86.0	91.0	86.0	140.0	77.5
Difference between FCH and PBO in median first 5-min BM (g)	13.0		22.5		-8.0		21.0		5.0		62.5	
Second 5-min BM (g), median	85.0	78.0	70.5	76.5	86.0	81.0	77.5*	54.0	73.0	50.0	101.0	75.0
Difference between FCH and PBO in median second 5-min BM (g)	7.0		-6.0		5.0		23.5		23.0		26.0	
Change in 5-min BM (second – first measurement) (g), median	-20.0	-18.0	-24.0	-15.5	-6.0	-29.0	-22.5	-21.5	-27.0	-28.0	-16.0	-4.5
Difference between FCH and PBO in median 5-min BM reduction (g)	-2.0		-8.5		23.0		-1.0		1.0		-11.5	

*$P < 0.05$ vs placebo.
5-min BM: 5-min bleeding mass; CTA: patients whose treatment was adherent with transfusion algorithm; FCH: fibrinogen concentrate human; ITT: intent-to-treat; non-CTA: patients whose treatment was not fully adherent with the transfusion algorithm; PBO: placebo.

The transfusion algorithm was adhered to in 104 patients (68.4%; CTA) and not adhered to in 48 patients (31.6%; non-CTA). In the FCH group, 31 patients were non-CTA (39.7%) including 7 reoperations, vs 17 (23.0%) in the placebo group with 3 reoperations. The difference between the 2 treatment groups in the CTA:non-CTA ratio was statistically significant ($P = 0.036$). Before administration of the study medication, 102 patients (69.4%) had plasma fibrinogen levels ≤2 g/l, and 45 (30.6%) >2 g/l. Seventy-one patients (46.7%) were 'early' patients at their study centre.

Significantly larger quantities of ABPs were given to non-CTA versus CTA patients ($P < 0.001$; Table 1), regardless of treatment. The median number of units transfused was higher with FCH than with placebo regardless of transfusion algorithm adherence. The first 5-min BM was higher in the FCH group than in the placebo group for intent-to-treat and CTA populations, but similar for non-CTA patients. A slightly greater median reduction in 5-min BM was observed with FCH versus placebo among CTA but not non-CTA patients.

Table 2 shows outcomes by pretreatment fibrinogen level and adherence to the transfusion algorithm. A numerically lower second 5-min BM with FCH versus placebo was seen only in CTA patients with a pretreatment plasma fibrinogen level ≤2 g/l; this was despite the median first 5-min BM being 22.5 g greater in the FCH group. In this group, median reduction in 5-min BM was 24.0 g with FCH and 15.5 g with placebo ($P = 0.071$). In contrast, FCH did not show efficacy benefits in CTA patients with pretreatment fibrinogen >2 g/l. The results in non-CTA patients were inconsistent. In all subgroups defined according to pretreatment fibrinogen level, ABP transfusion was numerically higher with FCH versus placebo.

As shown previously, there was considerable variation across pooled study centres for ABP transfusion and treatment protocol adherence. Adherence rates were higher in the Czech Republic (100%) and Japan (87.5%) versus those in other pooled centres (43–58%). Among the CTA patients, the largest differences between FCH and placebo in ABP transfusion were observed in the UK and the Czech Republic (FCH versus placebo: 4 vs 0 units transfused; Fig. 2). Correspondingly, these centres showed the largest differences between FCH and placebo in first 5-min BM (35 ml and 55 ml greater with FCH versus placebo in the UK and the Czech Republic, respectively). The reduction in the 5-min BM was larger with FCH versus placebo in CTA patients at 4/5 pooled centres (Fig. 2).

In 'early' patients, adherence to the transfusion algorithm was lower than in 'late' patients [62% (FCH 18/36, placebo 26/35) vs 74% (FCH 29/42; placebo 31/39); Table 3]. 'Early' FCH-treated patients had significantly higher first 5-min BM and ABP consumption than 'early' placebo patients, whereas BM reduction was similar between the study arms. 'Late' patients showed similar first 5-min BM and ABP consumption in the FCH and placebo groups, but a trend towards greater reduction of bleeding was observed in the FCH group. This trend became more pronounced when we considered the subsets of CTA patients and CTA patients with pretreatment fibrinogen levels ≤2 g/l, although statistical significance was not reached. Furthermore, in 'late' CTA patients with pretreatment fibrinogen ≤2 g/l, median ABP transfusion was numerically lower with FCH versus placebo (2 vs 4 units; $P = 0.573$).

Comparisons of REPLACE with the preceding phase II study are explored in Table 4 and Fig. 3. Distributions by surgical procedure show that comparable percentages of patients underwent thoracic aortic aneurysm repair with or without proximal arch

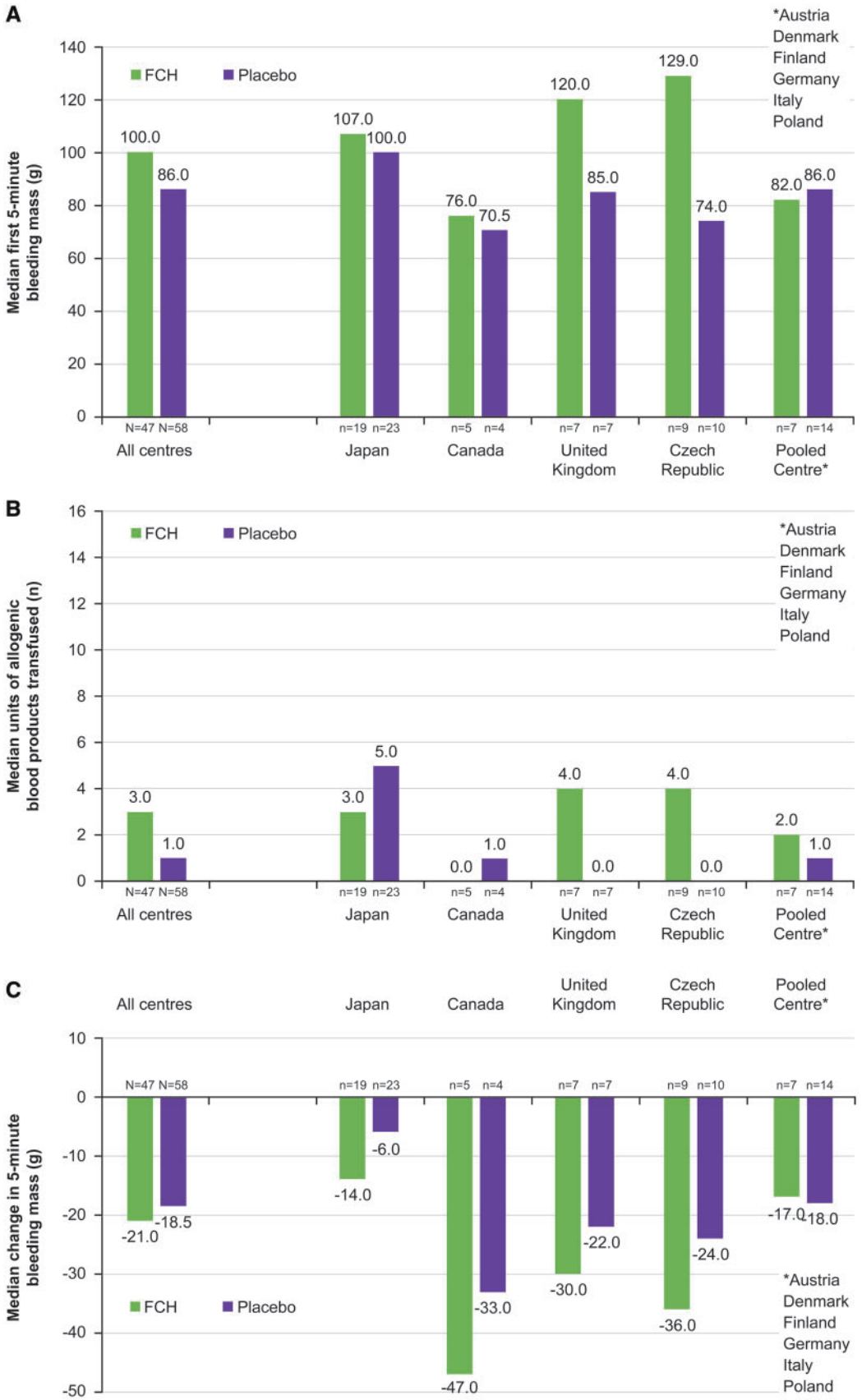

Figure 2: Results by pooled centres among patients whose treatment was adherent with the transfusion algorithm: first 5-min bleeding mass (5-min BM) (**A**); transfusion of allogeneic blood products over 24 h (**B**); median change in 5-min BM in response to study medication (second versus first 5-min BM) (**C**). FCH: fibrinogen concentrate human.

Table 3: Transfusion of allogeneic blood products and 5-min BM measurements according to number of patients previously treated at the study centre, adherence to transfusion algorithm and pretreatment fibrinogen level

	Early patients						Late patients					
	ITT		CTA		CTA with pretreatment fibrinogen ≤2 g/l		ITT		CTA		CTA with pretreatment fibrinogen ≤2 g/l	
	FCH (*N* = 36)	PBO (*N* = 35)	FCH (*N* = 18)	PBO (*N* = 26)	FCH (*N* = 13)	PBO (*N* = 16)	FCH (*N* = 42)	PBO (*N* = 39)	FCH (*N* = 29)	PBO (*N* = 31)	FCH (*N* = 15)	PBO (*N* = 22)
Allogeneic blood products, 24 h (median units transfused)	5.0*	1.0	4.0*	1.0	3.0	1.0	4.5	4.0	2.0	2.0	2.0	4.0
First 5-min BM (g), median	107.0*	90.0	107.0*	85.0	118.0*	82.5	96.0	94.0	91.0	89.0	100	92.5
Difference between FCH and PBO in median first 5-min BM (g)	17.0		22.0		35.5		2.0		2.0		7.5	
Second 5-min BM (g), median	83.0*	57.0	77.5	57.0	78.0	53.5	74.0	78.0	57.0	78.0	67.0	81.5
Difference between FCH and PBO in median second 5-min BM (g)	26.0		20.5		24.5		-4.0		-21.0		-14.5	
Change in 5-min BM (second – first measurement) (g), median	-20.0	-24.0	-25.5	-22.5	-31.0	-22.5	-19.0	-13.0	-21.0	-13.0	-21.0	-9.5
Difference between FCH and PBO in median 5-min BM reduction (g)	4.0		-3.0		-8.5		-6.0		-8.0		-11.5	

*$P < 0.05$ *vs* placebo.
5-min BM: 5-min bleeding mass; CTA: patients whose treatment was adherent with transfusion algorithm; early patients, those among the first 3 at their study site to be treated; FCH: fibrinogen concentrate human; ITT: intent-to-treat; late patients, those not among the first 3 at their study site to be treated; PBO: placebo.

and thoracoabdominal aortic aneurysm repair in the phase II study, whereas in REPLACE only a small percentage of patients underwent thoracoabdominal aortic aneurysm repair. Mean plasma fibrinogen levels before administration of the study medication were higher in REPLACE than in the phase II study; moreover, the percentage of patients with pretreatment fibrinogen levels >2 g/l was 3 times higher in REPLACE than in the phase II study. The percentage of randomized patients not meeting bleeding criteria for study inclusion was higher in REPLACE than in the phase II study. In REPLACE, 327 randomized patients (63%) exhibited 5-min BM <60 g vs 6 (7.5%) in the phase II study. A 51% reduction in 5-min BM was seen with FCH in the phase II study and only a 9% reduction with placebo. In comparison, a smaller reduction with FCH and a larger reduction with placebo was observed in REPLACE. The mean time from CPB cessation to the first 5-min BM was prolonged in REPLACE: 25.6 min (SD: 13.5 min) vs 11.3 min (SD: 7.9 min) in the phase II study (Fig. 3). The time between the end of the first and start of the second 5-min BM measurement was also prolonged in REPLACE.

DISCUSSION

REPLACE study results demonstrated a lack of efficacy benefit with FCH [20]. The current analyses show that the difference between the REPLACE results and those from the preceding phase II study, which reported efficacy benefits, may have been due to unavoidable differences in the study population, variation in FCH administration, and variation in adherence to the transfusion protocol.

Because pretreatment plasma fibrinogen levels >2 g/l were seen in 7% of patients in the phase II trial, it was assumed that few REPLACE participants would meet this criterion; however, 31% did, potentially limiting the FCH treatment effect. The results presented here support the hypothesis that FCH may be more effective in patients with plasma fibrinogen ≤2 g/l vs >2 g/l. FCH is licensed in Europe for use in acquired coagulation deficiencies with hypofibrinogenaemia [23], and fibrinogen supplementation is recommended for plasma fibrinogen levels <1.5–2 g/l [21, 24].

Due to reanalysis and inclusion of reoperations, the numbers of CTA and non-CTA patients differ slightly from those in the primary publication. Non-adherence to the transfusion algorithm may have increased data variability and decreased the likelihood of observing the true treatment effect of FCH. The percentage of non-CTA patients in the FCH group was higher than with placebo (40% vs 23%), which had a major impact on the rank-sum score. Also, adherence to the transfusion algorithm increased among 'late' versus 'early' patients. Because the effects of FCH were more evident in 'late' patients, investigators who treated more patients likely gained familiarity and proficiency with the protocol, enabling more accurate assessment of the FCH treatment effect. The protocol's complexity and the introduction of a study-specific transfusion algorithm led to increased deviations in 'early' patients. Also, at the start of the study, investigators may have had low confidence in the level of patient care provided by the protocol, leading to possible selection of more 'straightforward' patients (this could explain the high baseline fibrinogen levels in REPLACE versus the phase II study). Had the number of centres been 6–8 as planned, 18–24 'early' patients and ∼130 'late' patients would have been enrolled. The larger number of study centres meant fewer patients were enrolled at each site, resulting in 71 'early' and 81 'late' patients, which affected the data analysis.

Table 4: Comparison of results of the REPLACE trial with those from the preceding phase II study

	REPLACE			Preceding phase II study		
	FCH	Placebo	Total	FCH	Placebo	Total
Surgery type, *N* (%)						
TAA-	43 (55)	34 (46)	77 (51)	9 (31)	12 (38)	21 (34)
TAAA	3 (4)	4 (5)	7 (5)	8 (28)	10 (31)	18 (30)
TAA+	32 (41)	36 (49)	68 (45)	12 (41)	10 (31)	22 (36)
Pretreatment plasma fibrinogen level (assessed at end of CPB)						
Mean (g/l)	1.80	1.73		1.57	1.56	
≤2 g/l, *N* (%)	51 (67)	51 (72)	102 (69)	26 (90)	30 (97)	57 (93)
>2 g/l, *N* (%)	25 (33)	20 (28)	45 (31)	3 (10)	1 (3)	4 (7)
Randomized patients (%) not meeting bleeding criteria for study inclusion			322/519 (62)			15/80 (19)
Difference between median first and median second 5-min BM[a]	29 (27% reduction)	19 (21% reduction)		52 (51% reduction)	10 (9% reduction)	

[a]Differences between median values (as opposed to median changes, which are shown elsewhere) are provided here because the latter data are not available for the phase II study.

5-min BM: 5-min bleeding mass; CPB: cardiopulmonary bypass; FCH: fibrinogen concentrate human; TAA: thoracic aortic aneurysm; TAAA: thoracoabdominal aortic aneurysm.

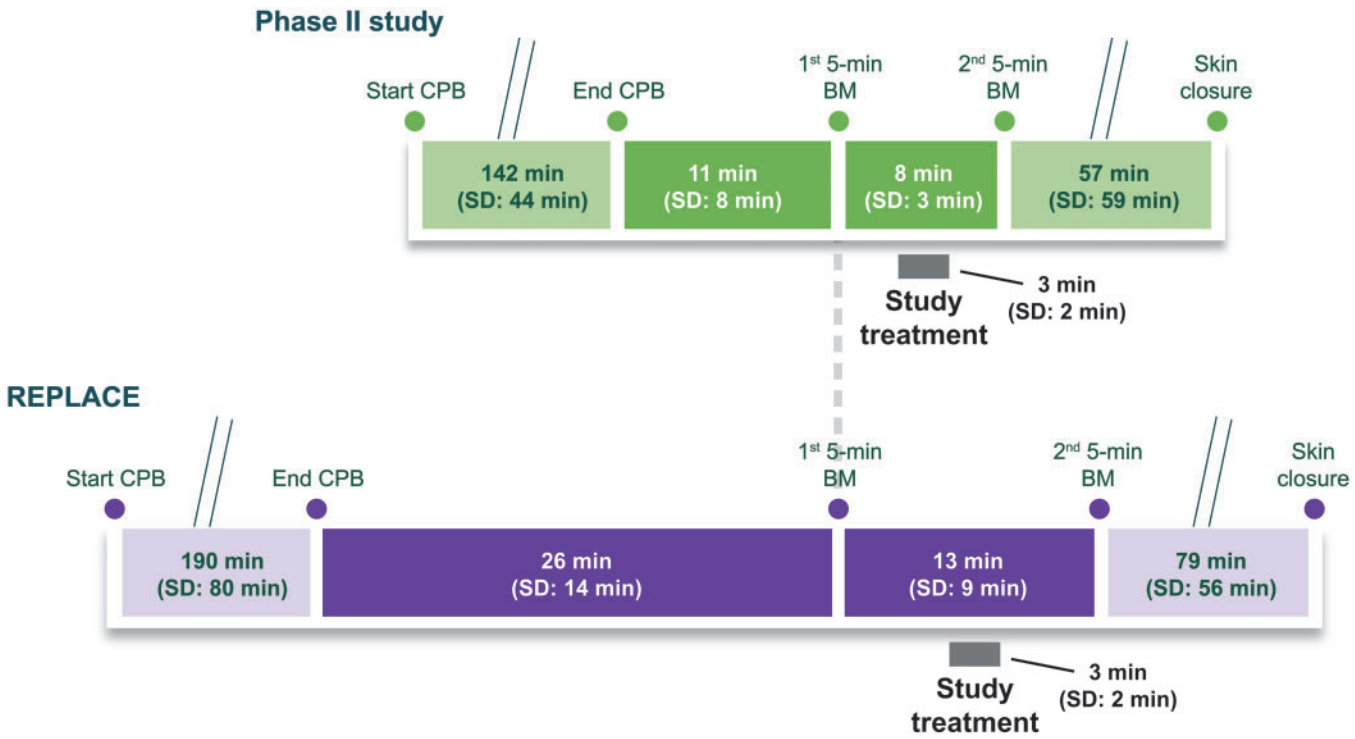

Figure 3: First and second bleeding mass: comparison with the preceding phase II study in relation to timing (mean, SD). BM: bleeding mass; CPB: cardiopulmonary bypass; SD: standard deviation.

With a greater number of patients at each site as originally planned, a complete rank sum per study site would have been possible. However, with an average of 4.6 patients per site, multiple sites had to be pooled for the analysis. With numerous causes of variability among the sites, the feasibility of a rank-sum score including several sites may be questioned. Future trials would likely benefit from reduced variability, either by increasing the numbers of patients included from each site (thus reducing the number of 'early' patients included) or reducing the number of sites used. However, the challenge of enrolling a sufficient number of patients using either of these options may mean that reducing this variability is not feasible.

Individually, none of the 3 patient stratifications explored provided a clear explanation for the REPLACE results. However, when considering adherence to the algorithm, baseline fibrinogen level, and previous study centre experience together, trends in favour of FCH were observed. This finding is not statistically robust due to the small number of patients meeting all 3 criteria. Potentially, a larger study would enable more definite conclusions to be drawn, as would changes in design to improve

adherence and target treatment of patients with low fibrinogen concentration.

The imbalance in pretreatment 5-min BM between the FCH and placebo groups may also have affected the REPLACE results. The median reduction needed to end the intraoperative transfusion regimen was 50% higher in the FCH arm. Study centres with the largest differences in first 5-min BM between the FCH and placebo groups showed the greatest disparities between the 2 arms in quantity of ABPs transfused; this imbalance in the 5-min BM is attributable to chance.

Efficacy benefits with FCH were observed in the preceding phase II study [12]; therefore, differences between it and REPLACE may be important. The extended time between CPB cessation and the first 5-min BM in REPLACE increased the opportunity for surgical haemostasis. In contrast, the 5-min BM assessment in the phase II study had been practised beforehand. There were also differences in patients' characteristics: in REPLACE, few patients underwent thoracoabdominal aortic aneurysm repair (a procedure associated with relatively high rates of ABP transfusions) and pretreatment fibrinogen levels were high. The high percentage of randomized patients not bleeding sufficiently in REPLACE versus in the phase II study indicates study population differences. Also, the algorithm-defined administration of ABPs differed between the studies.

Procedural differences between REPLACE and clinical practice may also be relevant. Fibrinogen was administered at a relatively high single dose in REPLACE. In clinical practice, initial treatment typically comprises a lower initial dose with the potential for further adjunctive treatment depending on clinical need and measurement of fibrinogen levels or fibrin-based clot strength. The low bleeding rates observed in REPLACE do not reflect those observed in routine clinical practice [25, 26], where 5-min BM is rarely used and prethawed plasma and platelets are not routinely available in the operating room (in REPLACE, prethawed ABPs were available to minimize delay of haemostatic therapy in the placebo arm).

Limitations

The limited number of patients in the original trial introduced the potential for a type II error in the subsequent primary analysis. The present analyses have some limitations. Firstly, the original study was not powered for the smaller numbers of patients in the subgroup analyses. Secondly, the subgroups were based on arbitrary definitions. Non-CTA patients are a disparate group; some required reoperation and the algorithm was deliberately abandoned in others. Also, different cut-off points for pretreatment fibrinogen levels and numbers of patients previously treated at each site could have been chosen. Nevertheless, the present data are helpful in understanding the REPLACE results.

CONCLUSION

In conclusion, REPLACE study outcomes may have been influenced by adherence to the transfusion algorithm, patients' pretreatment fibrinogen levels and investigators' familiarity with implementing the protocol. There were also several important differences between the multicentre REPLACE study and the preceding single-centre phase II study, which reported efficacy benefits with FCH versus placebo. Together, this variability might explain the differences in results with regards to ABPs between the phase II and REPLACE studies and may help inform the design of future studies of FCH in patients undergoing cardiac surgery.

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Conflict of interest: Niels Rahe-Meyer serves on steering committees and advisory boards and is principal investigator for CSL Behring and Merck. Jerrold H. Levy serves on steering committees for Boehringer Ingelheim, CSL Behring, Grifols, Instrumentation Laboratories and Pfizer. C. David Mazer has received research support and honoraria from Allocure, Boehringer Ingelheim, CSL Behring, Fresenius Kabi, Medicines Company, Octopharma and Quark and is on the editorial board of the *Canadian Journal of Anesthesia*. Alexey Schramko has received honoraria from CSL Behring, Grifols, B. Braun, and Fresenius Kabi and educational grant funding from Orion. Andrew A. Klein has received educational grant funding, honoraria or travel funding from CSL Behring, Brightwake Ltd, Pharmacosmos, Vifor Pharma and Masimo. Radim Brat and Yutaka Okita have nothing to disclose. Yuichi Ueda serves on steering committees for CSL Behring in Japan and has received honoraria from CSL Behring for consultation. Dirk Steffen Schmidt is a full-time employee and shareholder of CSL Behring. Ravi Gill serves on steering committees for CSL Behring, serves on advisory boards for Octapharma, and has been paid to speak on behalf of CSL Behring, Octapharma and Roche.

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